# Marfan Syndrome

## Overview

Marfan syndrome (MFS) is an autosomal dominant genetic disorder which affects the connective tissues. MFS most commonly affects the heart, eyes, blood vessels and skeleton. It was first described as a congenital defect in interstitial tissues by Dr Antoine Marfan, a French paediatrician, in 1896. As the affected bones caused long and slender (spider-like), it was also called 'spider finger/toe syndrome'. Other doctors subsequently supplemented with changes in eye and hearts, and family history, substantiating it into a complete syndrome.

## Pathogenesis

Most MFS patients are familial. On the other hand, about 15–30% of all cases are due to *de novo* genetic mutation. The mutation rate is around ½ per 10,000. MFS is an autosomal dominant disease with 90% was caused by mutation in the *FBN1* on chromosome 15, which encodes for fibrillin 1 (an elastin-matrix glycoprotein). A small proportion of cases are caused by the mutation of transforming growth factor-beta receptor (TGF-β receptor). In MFS patients, around 600 mutation sites were discovered, and widely distributed across the whole are area the *FNB1* gene. Most of the mutations are mis-sense mutations or splice site mutations, mostly results in loss of function of protein. Fibrillin 1 is essential for formation of elastic fibre of connective tissues, which distributes throughout will lead to aortic dilatation, aortic dissection or even rupture, and multi-system failure due to generalized dysplasia of mesoderm tissues.

The incidence rate of MFS is 1/5000-1/3000, affecting both sexes equally, regardless of geography. However, gender can cause difference in the clinical manifestation as males are 40% more susceptible to dilatation of the ascending aorta and other vascular incidences.

## Clinical manifestation

MFS patients may have presentations of the following systems:

**Cardiovascular system**

- Aortic root dilation
- Aortic valve incompetence
- Aortic dissection
- Mitral valve prolapse with or without incompetence
- For MFS caused by *FBN1* mutation, the prevalence of ascending aorta dilatation increases with age; from the age of 30 to 60, the prevalence increases from 53% to 96%. The patients may present as shortness of breath, chest pain, palpitation, dizziness, syncope or haemoptysis.
- Physical examination:
    1. Heart boarder enlarged leftward and downward. By auscultation, systolic murmur at mitral valve, diastolic biphasic murmur at aortic valve can be

detected. Signs of peripheral vascular disease and heart failure can also be observed.

2. Skeleton features: tall and slender build, thin and long fingers and toes, arm span more than their body height, scoliosis, kyphosis, pectus excavatum or pectus carinatum, hypermobility of joints (arthrochalasis), fallen arches (flat feet) etc.
3. Eye abnormalities: eye lesions account for 50%-70% (?), including flattened cornea, elongated eyeballs, retinal detachment, cataract, lens dislocation or partial dislocation, iridodonesis (or mild, vibration of the iris with eye movement), ectopia lentis (原文為瞳孔移位,ectopia lentis 為晶體移位).
4. Others: dural ectasia hernias, striae atrophicae (stretch mark), recurrent hernias or incision hernia, high arched palate etc.

## Investigations:

1. Electrocardiogram: no specific ECG change, can be complicated with different forms of arrhythmia.
2. Chest X-ray: enlarged left ventricle, or symmetrical enlarged cardiac shadow, aortic configuration of the heart, widening of the ascending aorta, enlarged aortic knob, prominent aortic arch, relatively depressed pulmonary artery, pulmonary congestion.
3. Skeleton X-ray: slender bones of limbs, osteoporosis, thin cortices, slender metatarsophalanx and metacarpal phalanx, scoliosis, kyphosis, spina bifida, absence of dura mater.
4. Echocardiography: aortic root and/or ascending aorta enlargement, aortic valve regurgitation or mitral valve prolapse.
5. Eye examination: dislocation of lens.
6. CT, MRI and cardiovascular imaging: enlarged left ventricle, mitral valve prolapse, aortic valve regurgitation, aneurysm of the ascending aorta, aortic dissection, abdominal aortic aneurysm etc.
7. DNA tests: the detection of *FBN1* or *TGBR1/2* mutation helps the diagnosis of MFS.

## Diagnosis:

The 2010 Revised Ghent Nosology is commonly used. The diagnosis is made according to family history, clinical signs, imaging (echocardiography), eye examination (slit lamp examination) and DNA testing.

1. Patients with no MFS family history but have any one of the conditions below can be diagnosed with MFS.

    a. Z score of aortic root ≥ 2 or aortic root dissection, dislocation of lens, and excluding Sphrintzen-Goldberg Syndrome, Loeys-Dietz Syndrome and vascular Ehlers-Danlos Syndrome or similar conditions and related genetic mutation.
    b. Z score of aortic root ≥ 2 or aortic root dissection and detected disease-causing *FBN1*genetic mutation.
    c. Z score of aortic ≥ 2 or aortic root dissection, system scoring ≥7, and excluding Sphrintzen-Goldberg Syndrome, Loeys-Dietz Syndrome and vascular Ehlers-Danlos Syndrome or similar conditions and related genetic mutation.

d. Dislocation of lens associated with aortic aneurysm, and detected disease-causing *FBN1* genetic mutation.

2. Patients with family history of MFS, diagnosis can be made if any one of the conditions below is fulfilled.

    a. Lens dislocation
    b. System scoring ≥7 and excluding Sphrintzen-Goldberg Syndrome, Loeys-Dietz Syndrome and vascular Ehlers-Danlos Syndrome or similar conditions and related genetic mutation.
    c. Z score of aortic root ≥ 2 (above the age of 20) or ≥3 (below the age of 20), or aortic root dissection, and excluding Sphrintzen-Goldberg Syndrome, Loeys-Dietz Syndrome and vascular Ehlers-Danlos Syndrome or similar conditions and related genetic mutation.

3. If the system score reaches 7, it is worth considering diagnosis.

    Table 1. System scoring for each condition

| Condition | Scores |
|---|---|
| Steinberg's thumb sign and Walker's wrist sign | 3 (1 if only one condition) |
| Pectus carinatum | 2 |
| Pectus excavatum | 1 |
| Hindfoot deformity | 2 (1 if flat feet) |
| History of pneumothorax | 2 |
| Dural ectasia hernias | 2 |
| Protrusion of the acetabulum (Protrusio acetabuli) | 2 |
| Reduced ratio of height of upper segment/lower segment of the body, increase of arm span to height ratio but no scoliosis | 1 |
| Scoliosis or thoracolumbar kyphosis | 1 |
| Decrease of elbow joint abduction | 1 |
| Facial signs: ultradolichocephalis (long head) , enothalmus, dropping of palpebral fissure, malar bone anomaly, maxillary/mandibular retrognathia) | 1 (if three of the signs matches) |
| Myopia reaches -3.00 dioptres | 1 |
| Mitral valve prolapse | 1 |
| Striae | 1 |

# Differential diagnosis

MFS need to be differentiated with the diseases below:

- Familial aortic aneurysm and aortic dissection syndrome
- Congenital contractual arachnodactyly

- Mitral valve prolapse syndrome
- Lens dislocation syndrome
- Loeys-Dietz syndrome
- Weill-Marchesani syndrome
- Sphrintzan-Goldberg syndrome
- Ehlers-Danlos syndrome
- Stickler syndrome
- Congenital bicuspid/aortic valve lesion with aortic lesion
- Homocystinuria
- MASS phenotype (mitral valve prolapse, diameter of aortic root at upper limit of normal range, skin change, scoliosis, anomaly of thoracic cavity, joint hypermobility.)

# Treatments:

95% of deaths in MFS are caused by the dysfunctions of the cardiovascular system – aortic dissection, rupture and heart failure. Therefore, special attention must be paid to aortic lesions is needed. MFS treatment includes general, medical and surgical treatments.

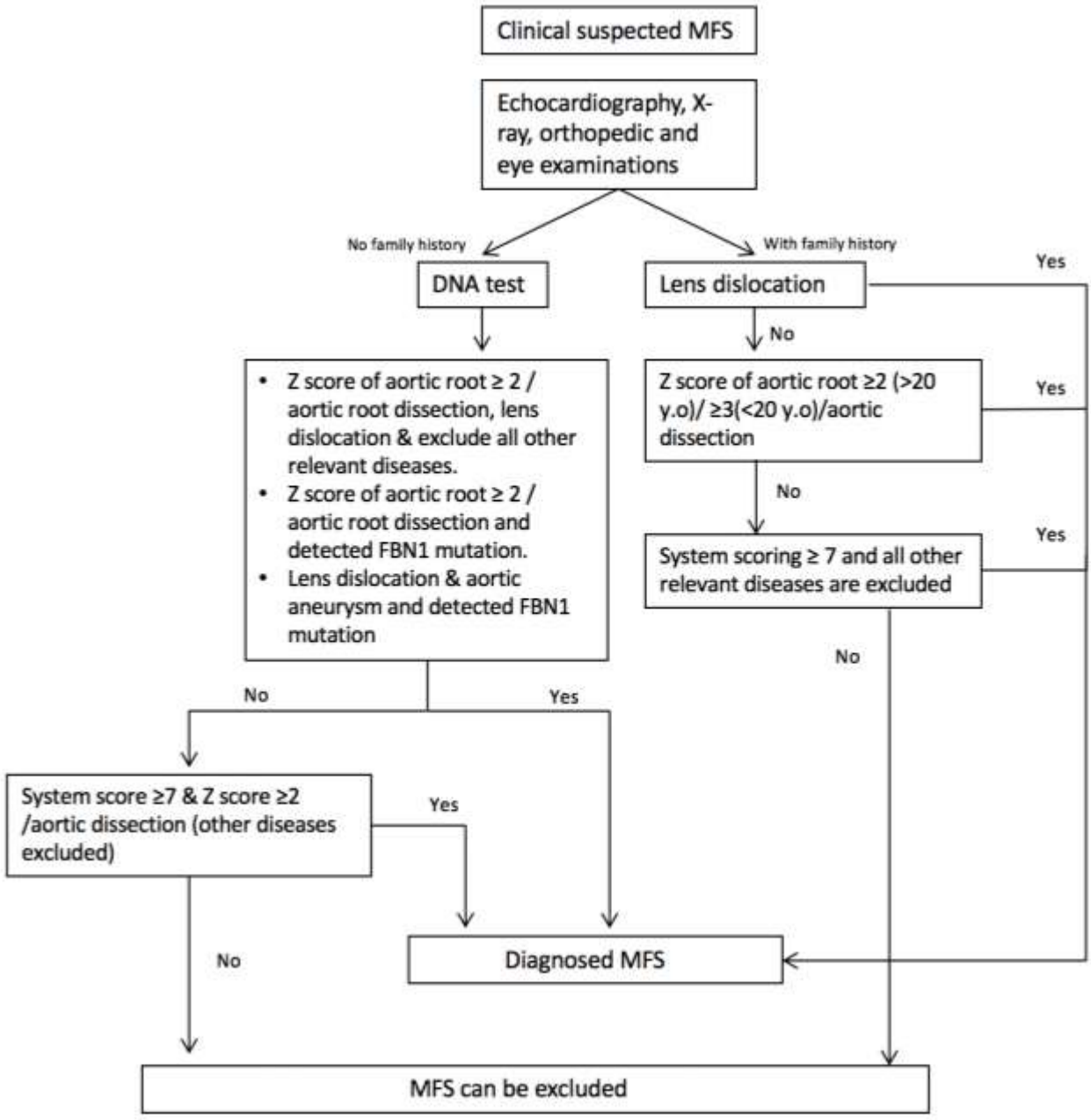
1. General treatment
    a. Monitoring of the aorta: MFS patients should be monitored with echocardiography 6 months after diagnosis to confirm the diameters of the aortic root and ascending aorta, and the velocity of increase of these diameters. The frequency of monitoring afterwards depends on the aortic diameters and velocity of increase in diameters.
    b. Limitation of vigorous activities: most MFS patients can participate in low to medium intensity exercises. Contact sport and over exercise, especially isometric exercise involving Valsalva maneuver, should be avoided.

2. Medical treatment
    a. Beta blocker: recommended for adults and children, in order to slow down the speed of aortic enlargement, unless contraindicated.
    b. Angiotensin II receptor antagonist (ARB): recommended to be used on top of beta blocker, according to the patient's tolerance, in order to slow down the speed of enlargement of the aortic root.

3. Surgical treatment
    a. The 2010 ACC/AHA/AATS guideline suggested that when a MFS the diameter of patient's aorta reaches ≥ 50mm, an elective aortic root replacement surgery is recommended in order to avoid acute dissection or rupture. If when the diameter of the aorta is <50mm, the indication for surgical repair include: rapid widening of diameter (>5mm/year), family history of aortic dissection at aortic diameter of less than 50mm, or progressive aortic valve incompetence. For severe mitral valve incompetence, if there are associated symptoms or signs of progressive left ventricle enlargement or left ventricular systolic dysfunction, mitral valve repairment or replacement is recommended.
    b. MFS patients are advised to have an eye examination annually. Eye treatments including correction of myopia, photocoagulation or lens extraction are suggested for laceration or detachment of retina.

c. Surgery can be offered to correct scoliosis, if the curvature is more than 40 °. Surgeries can also be considered for severe anomalies of the thoracic cavity, recurrent pneumothorax and arthrosis due to laxity of the joints.

## Diagnostic Algorithm



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